What's New in the Field of Immunization

JOHN J. MILLER, JR., M.D., *San Francisco*

IN the field of immunization there have been a number of recent developments which are worthy of discussion. Mumps can be added to the list of diseases which in the future may be prevented. The studies of Stokes, Enders, and their associates[27,5] are encouraging. In experiments, formolized mumps virus from monkey parotid glands protected about 50 per cent of children against infection. Attenuated virus from egg passage may eventually prove to be the answer.

The somewhat precarious status of two older immunization procedures has been altered in the past year. The outlook for successful immunization against influenza has become less promising. Contrary to earlier studies made in United States Army camps, three field trials reported during the past year yielded no evidence of protection.[6,30,26] These failures are in the main accounted for by the appearance of new strains of virus antigenically distinct from those incorporated in commercial vaccines. Unfortunately, there is also reason to believe that new strains will continue to appear. As the immunity conferred is apparently almost strain-specific, vaccines in the future either must be highly polyvalent or broadly antigenic, or may even have to be produced rapidly in the face of a spreading epidemic after the infecting strain has been isolated. The one cheerful aspect of the present status of vaccination against influenza is the likelihood that calcium phosphate adsorbed vaccine[25] will produce a firmer and more lasting immunity than do the currently available unadsorbed products.

The controversial status of BCG vaccination against tuberculosis, on the other hand, seems to be resolving. Recent reports from the Indian reservation,[1] from Denmark,[12] and from Chicago,[22] have demonstrated that decreased morbidity and mortality rates can be obtained with some preparations of vaccine. The evidence has been considered sufficiently valid by the United States Public Health authorities to lead them to commence further field studies and to attempt laboratory standardization of the vaccine.[29] The Surgeon General's office, however, does not feel that BCG vaccine should be made commercially available at present. Public health officials desiring to set up controlled studies should contact the office of the Tuberculosis Control Division of the U. S. Public Health Service and obtain vaccine through this channel.

Now, a word about the oldest immunization procedure. There is widespread and misplaced confidence in the validity of the "immune reaction" to cowpox vaccine. It has long been known[4] that local erythema and induration appearing in 24 hours may result from inoculation with dead virus in an individual allergic to calf lymph. Nevertheless, the occurrence of smallpox in American and British soldiers with records of recent "immune reactions" has jolted our complacency.[4] Leake in the U. S. Public Health Service handbook on vaccination[16] describes the "early reaction" as one in which "the broadest redness is reached in 8 to 72 hours after vaccination." There is "a slight elevation of the skin . . . and usually no vesicle." He then goes on to state that "such a reaction should not be called a reaction of immunity unless fully potent vaccine has been used." But how are we to know our vaccine is fully potent? The only answer is: By observing instances of primary local vaccinia following inoculation with the same lot of vaccine at about the same time. The best that we can do, then, is to obtain new lots of vaccine frequently and always keep them in the freezing chamber of a refrigerator.

In diphtheria immunization there are still problems—that of the susceptible adult and that of the individual who is sensitive to the toxoid. Commonly these two problems coexist. Toxoid sensitivity tests are essential before toxoid is given to adolescents and to adults. It is possible that the sublingual application of toxoid tablets[2,20] will in the future prove of value in reimmunizing the toxoid-sensitive adult.

In the field of pertussis immunization there has been no substantial contribution since Sako and his coworkers[24,23] showed that infants under three months of age could be actively immunized. The question of whether precipitated vaccine is necessary for immunization at this age has not been settled.

Active immunization against tetanus has such a splendid war record that unwarranted statements have appeared in the literature. It has been said that when a previously actively immunized individual is wounded, all one need do is to give him a "booster" of tetanus toxoid. This complete confidence in primary immunization and in the secondary anamestic response requires a dash of cold water, in my opinion. The very great protection against tetanus obtained by the armed forces was in men very recently immunized. The majority of troops also had had routine annual "booster" reinjections.

The effect of the lapse of time on the speed of the response to reinjection of toxoid is not well known. Contrary to the reports of others,[21,19] we have observed that with the passage of time the speed of response is decreased. In some individuals, after an interval of five years or more since the last previous injection there may be no detectable antitoxin seven days after the reinjection. Furthermore we have observed that children basically immunized with pre-

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From the Department of Pediatrics, Stanford University School of Medicine, San Francisco, California.

cipitated or adsorbed toxoid respond to a "booster" faster than do those basically immunized with fluid toxoid. Thirdly, and on the other hand, fluid toxoid produces a more rapid increase in antitoxin than does precipitated toxoid in children basically immunized with the latter. In other words the immunization mechanism is sensitized better by a slowly absorbed antigen but is stimulated faster by a rapidly absorbed antigen.

One may ask, "Are these measurements of antitoxin significant?" I believe so, for the following reasons. Let us examine the few cases of tetanus that did occur in immunized soldiers during the recent war. A total of 28 cases have been reported from the British and American armies.[3,17] All cases occurred after severe wounding, and almost all occurred after unusually short incubation periods—the shortest was two days. The fatality rate in these few cases was surprisingly high, 50 per cent. Apparently what occurred was that active immunization prevented tetanus in everyone except those suffering from massive intoxication following severe wounding. Here the incubation period was too short for a booster to stimulate antitoxin production. When the British gave prophylactic antitoxin in such cases, they obtained a lower fatality rate than we did with toxoid "boosters."

If both antitoxin and toxoid could be administered in such severe cases, would both immediate and delayed protection result? From evidence obtained in our laboratory, I believe so. Studies following the simultaneous administration of antitoxin and toxoid in different extremities of previously immunized animals indicate that the secondary immune response, unlike the primary immune response, is not prevented by circulating heterologous antitoxin. In summary, then, it would appear that maximal protection against tetanus can best be obtained by (a) inducing basic immunity with precipitated toxoids, (b) maintaining high levels of antitoxin with routine biennial reinjections of precipitated toxoids, and (c) employing rapidly absorbed fluid toxoid when wounding occurs. In cases of compound fractures or other wounds likely to be massively contaminated, or in cases in which the interval since the last toxoid injection is five years or more, prophylactic antitoxin should probably be administered in addition to the booster at the time of wounding.

In regard to passive immunization procedures, what's new, of course, is gamma globulin. In addition to being highly effective, and the agent of choice, in the prevention of measles, it has been employed in three other virus diseases. In mumps it is apparently not effective unless prepared from mumps convalescent serum,[8] which is not commercially available. On the other hand, ordinary gamma globulin from normal adult serum has been reported to confer protection against chickenpox.[7] Should this be confirmed, we will have a very useful agent in protecting sick infants and children exposed in hospitals.

In epidemic and endemic viral hepatitis ordinary gamma globulin is effective if administered during the first two weeks after exposure. Its great value was clearly demonstrated in two institutional epidemics[28,11] and in a large epidemic among our troops in Italy.[9] The dose for children is 0.22 cc. per kg. of body weight.

The importance of preventing the spread of epidemic hepatitis in troops at war or in children in an institution is obvious. But should we attempt to protect the child who has been exposed at home or in school? An attack of viral hepatitis produces immunity which is not strain-specific.[10] On the other hand, there is now ample evidence[15] that this disease is not always benign. Fatal cases are extremely rare but permanent liver damage may result.[18] Repeated needling of the liver for biopsy specimens is reported to have shown transition from acute hepatitis to cirrhosis in a few instances.[14] Fortunately for pediatricians, chronic liver disease following hepatitis is far more common in adults than in children.[13] Nevertheless we have recently observed a case of portal cirrhosis in a 12-year-old boy who had had an attack of typical catarrhal jaundice nine months previously. No other possible contributory factor was found. It is my opinion that although the dangers of infectious hepatitis are remote in childhood, this preventable disease should be prevented by passive immunization whenever possible.

REFERENCES

1. Aronson, J. D., and Palmer, C. E.: Experience with BCG vaccine in the control of tuberculosis among North American Indians, Pub. Health Reports, 61:802-820 (June 7), 1946.

2. Bousfield, G.: Restoration of diphtheria immunity without injections, Brit. M.J., 1:833-835 (June 16), 1945.

3. Boyd, J. S. K.: Tetanus in African and European theatres of war 1939-45, Lancet, CCL:113 (Jan. 26), 1946.

4. Edsall, G.: Active immunization, New England J. Med., 235:328-336 (Sept. 5), 1946.

5. Enders, J. F., Levens, J. H., Stokes, J., Maris, E. P., and Berenberg, W.: Attenuation of virulence with retention of antigenicity of mumps virus after passage in the embryonated egg, J. Immunol., 54:283-291 (Nov.), 1946.

6. Francis, T., Jr.; Salk, J. E., and Quilligan, J. J.: Experience with vaccination against influenza in the spring of 1947, Am. J. Public Health, 37:1013-1016 (Aug.), 1947.

7. Funkhouser, W. L.: The use of serum gamma globulin antibodies to control chickenpox in a convalescent hospital for children, J. Pediat., 32:257-259 (March), 1948.

8. Gellis, S. S., McGuinness, A. C., and Peters, M.: A study of the prevention of mumps orchitis by gamma globulin, Am. J. Med. Sci., 210:661-664 (Nov.), 1945.

9. Gellis, S. S., Stokes, J., Jr., Brother, G. M., Hall, W. M., Gilmore, H. R., Beyer, E., and Morrissey, R. A.: The use of human immune globulin (gamma globulin) in infectious hepatitis in the Mediterranean theatre of operations, J.A.M.A., 128:1062-1063 (Aug. 11), 1945.

10. Havens, W. P.: The etiology of infectious hepatitis, J.A.M.A., 134:653-655 (June 21), 1947.

11. Havens, W. P., Jr., and Paul, J. R.: Prevention of infectious hepatitis with gamma globulin, J.A.M.A., 129:270-272 (Sept. 22), 1945.

12. Holm, J.: BCG vaccination in Denmark, Pub. Health Reports, 61:1298-1315 (Sept. 6), 1946.

13. Horstman, D. M., Havens, W. P., and Deutsch, J.: Infectious hepatitis in childhood, J. Pediat., 30:381-387 (April), 1947.

14. Krarup, N., and Roholms, K.: Development of cirrhosis of the liver after acute hepatitis, elucidated by aspiration biopsy, Acta Med. Scand., 108:306-331, 1941.

15. Kunkel, H. G., Labby, D. H., and Hoagland, C. L.: Chronic liver disease following hepatitis, Ann. Int. Med., 27:202-219 (Aug.), 1947.

16. Leake, J. P.: Questions and answers on smallpox and vaccination, Reprint No. 1137 from Public Health Reports, Revised, 1946.

17. Long, A. P., and Sartwell, P. E.: Tetanus in the U. S. Army in World War II, Bull. U. S. Army M. C., 7:371 (Apr.), 1947.

18. Mallory, T. B.: Abstract of discussion on diseases of the liver, J.A.M.A., 134:678 (June 21), 1947.

19. McBryde, A., and Poston, M. A.: Immunization with tetanus toxoid, J. Pediat., 28:692-696 (June), 1946.

20. Mosucci, P., Gold, H., and De Falco, R. J.: Restoration of diphtheria immunity without injections (Bousfield's method), J. Pediat., 32:35-38 (Jan.), 1948.

21. Peshkin, M. M.: Immunity to tetanus induced by a third dose of toxoid four years after basic immunization, Am. J. Dis. Child., 69:83-88 (Feb.), 1945.

22. Rosenthal, S. R., Leslie, E. I., and Loewinsohn, E.: BCG vaccination in all age groups, J.A.M.A., 136:73-79 (Jan. 10), 1948.

23. Sako, W.: Studies on pertussis immunization, J. Pediat., 30:29-40 (Jan.), 1947.

24. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S.J.: Early immunization against pertussis with alum precipitated vaccine, J.A.M.A., 127:377-384 (Feb. 17), 1945.

25. Salk, J. E.: Studies on the antigenicity in man of calcium phosphate adsorbed influenza vaccine, J. Immunol., 57:301-322 (Dec.), 1947.

26. Sigel, M. M., Shaffer, F. W., Kirber, M. W., Light, A. B., and Henle, W.: Influenza A in a vaccinated population, J.A.M.A., 136:437-441 (Feb. 14), 1948.

27. Stokes, J., Jr., Enders, J. F., Maris, E. P., and Kane, L. W.: Immunity in mumps. VI. Experiments on the vaccination of human beings with formolized mumps virus, J. Exp. Med., 84:407-428 (Nov.), 1946.

28. Stokes, J., Jr., and Neefe, J. R.: The prevention and attenuation of infectious hepatitis by gamma globulin, J.A.M.A., 127:144-145 (Jan. 20), 1945.

29. Report of a conference on BCG vaccination, U. S. Public Health Service: Pub. Health Reports, 62:346-350 (Mar. 7), 1947.

30. Van Ravenswaay, A. C.: Prophylactic use of influenza virus vaccine, J.A.M.A., 136:435-437 (Feb. 14), 1948.

QUESTIONS AND ANSWERS

Question: Why not three doses of toxoid for basic immunity?

DR. MILLER: There is evidence that basic courses of three injections of precipitated tetanus toxoid induce higher and more enduring titers of antitoxin than do courses of two injections.

Question: Is not a recall injection of toxoid preferable to antitoxin?

DR. MILLER: Yes, indeed, for thereby sensitization to horse serum is avoided. A recall injection of toxoid can be relied upon and should be employed in previously immunized individuals for all puncture wounds and common lacerations. As I have already stated, antitoxin need be considered only in cases of compound fractures, massively contaminated wounds, shock (in which the immune response may be impaired), and when the interval since the last injection of toxoid is five years or more. Under these conditions I believe antitoxin should be administered in addition to toxoid. The antitoxin will afford immediate passive protection against short incubation period tetanus while the patient's immune mechanism is mobilizing his own antitoxin.

Question (Moderator): How much antitoxin, Dr. Miller?

DR. MILLER: Five thousand units if the patient is in shock, or severely wounded. Fifteen hundred units if the time interval since the last injection of toxoid is five years or more and the wound is not severe.